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9120306.7 **24 September 1991 (24.09.91) GB**(71) Applicant (*for all designated States except US*): **ALLERGAN INC. [US/US]; 2525 Dupont Drive, Post Office Box 19534, Irvine, CA 92713-9534 (US).**

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(57) Abstract

The invention provides for the use of a presynaptic neurotoxin (for example a bacterial neurotoxin such as botulinum toxin A) for the manufacture of a medicament for the treatment of cerebral palsy in juvenile patients. The juvenile patients are preferably juveniles of up to 6 years in age.

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**Method and Compositions for the
Treatment of Cerebral Palsy**

The present invention relates to the treatment of cerebral palsy in a juvenile patient and in particular to the promotion of normal muscle growth in a juvenile patient suffering from dynamic contractures caused by cerebral palsy.

Cerebral palsy is a collective name given to a range of conditions caused by brain injury caused at or around the time of birth, or in the first year of an infant's life. The brain injury may be caused, for example, by trauma during delivery. It may also arise through such causes as trauma due to road traffic accidents or meningitis during the first year of life. It has been found that there is an increased risk of cerebral palsy in prematurely born babies and, as a result of the improvements in technology which enable premature babies to be kept alive from a much earlier age, the incidence of cerebral palsy in many countries is actually increasing

rather than falling.

Although the brain injury causing cerebral palsy is a non-progressive injury, its effects may change as the sufferer grows older. The largest group of sufferers from cerebral palsy suffer from spastic cerebral palsy. Spastic cerebral palsy is characterised by dynamic contractures of the muscles which impair or inhibit completely the sufferer's ability to use his or her muscles. Moreover, muscle growth is impaired such that the longitudinal muscles become shorter relative to their associated bones as the infant grows older. Where the leg muscles are affected, the mobility of the sufferer can be severely reduced. Conventional attempts to cure this defect and to restore a measure of normal mobility typically have involved surgical intervention to alter the lengths of the tendons once the stage has been reached at which the knee joint can no longer be straightened or the sufferer can only walk on tiptoe.

There remains a need for a treatment which allows the longitudinal muscles to grow normally, thereby removing, or at least minimising the need to resort to surgical intervention. Moreover, there remains a need for a treatment which can augment surgical intervention to improve the mobility of the sufferer.

A bacterial toxin, botulinum toxin, has been used in the treatment of a number of conditions involving muscular spasm, for example blepharospasm, spasmodic torticollis (cervical dystonia), oromandibular dystonia and spasmodic

dysphonia (laryngeal dystonia). The toxin binds rapidly and strongly to presynaptic cholinergic nerve terminals and inhibits the exocytosis of acetylcholine by decreasing the frequency of acetyl choline release. This results in paralysis, and hence relaxation, of the muscle afflicted by spasm.

The term Botulinum toxin as used herein is a generic term embracing the family of toxins produced by the anaerobic bacterium *Clostridium botulinum* and, to date, seven immunologically distinct toxins have been identified. These have been given the designations A, B, C, D, E, F and G. For further information concerning the properties of the various botulinum toxins, reference is made to the article by Jankovic & Brin, *The New England Journal of Medicine*, pp 1186-1194, No 17, 1991 and to the review by Charles L Hatheway, Chapter 1 of the book entitled *Botulinum Neurotoxin and Tetanus Toxin* Ed. L. L. Simpson, published by Academic Press Inc. of San Diego CA 1989, the disclosures in which are incorporated herein by reference.

The neurotoxic component of botulinum toxin has a molecular weight of about 150 kilodaltons and is thought to comprise a short polypeptide chain of about 50 kD which is considered to be responsible for the toxic properties of the toxin, and a larger polypeptide chain of about 100 kD which is believed to be necessary to enable the toxin to penetrate the nerve. The "short" and "long" chains are linked together by means of disulphide bridges.

The neurotoxic polypeptide component is present in a complex with non-toxic proteins and haemagglutinins, the molecular weight of the complex being in the region of 900 kD.

Botulinum toxin is obtained commercially by establishing and growing cultures of *C. botulinum* in a fermenter and then harvesting and purifying the fermented mixture in accordance with known techniques.

The "A" form of botulinum toxin is currently available commercially from several sources, for example from Porton Products Ltd UK under the tradename "DYSPORE", and from Allergan Inc, Irvine, California under the trade name "OCULINUM".

It has now been found by the present inventor that children suffering from cerebral palsy related dynamic muscle contractures exhibit improvements in function following treatment with botulinum toxin and that such functional improvements persist when the tone reducing effects of the toxin have worn off.

It has also been found that by administering botulinum toxin to a juvenile spastic mammal during its growth phase, the consequent reduction in tone of the spastic muscle enables increased longitudinal growth of the muscle to take place.

In a first aspect, the present invention provides a method of treating a juvenile patient suffering from arrested muscle growth arising from the presence of dynamic contractures of the muscle, which method comprises

administering to the patient a therapeutically effective amount of a substance which blocks the release of synaptic vesicles containing acetylcholine.

The present invention also provides a method of treating a juvenile patient suffering from cerebral palsy, which method comprises administering to the patient a therapeutically effective amount of a substance which blocks the release of synaptic vesicles containing acetylcholine.

In a further aspect the invention provides a method of treating a juvenile patient suffering from arrested muscle growth arising from the presence of dynamic contractures of the muscle, which method comprises administering to the patient a therapeutically effective amount of a presynaptic neurotoxin, for example a bacterial neurotoxin such as botulinum toxin.

In a still further aspect the invention provides a method of treating a juvenile patient suffering from arrested muscle growth due to cerebral palsy, which method comprises administering a presynaptic neurotoxin (for example a bacterial neurotoxin such as botulinum toxin) to the patient in a non toxic amount sufficient to reduce muscle tone and promote improved muscle growth.

The botulinum toxin used according to the present invention preferably is Botulinum toxin A. Botulinum toxin A is available commercially from Porton Products Limited, UK, and from Allergan Inc, Irvine, California.

Administration of the toxin preferably is by means of

intramuscular injection directly into a spastic muscle, in the region of the neuromuscular junction, although alternative types of administration (e.g. sub-cutaneous injection) which can deliver the toxin directly to the affected muscle region may be employed where appropriate. The toxin can be presented as a sterile pyrogen-free aqueous solution or dispersion and as a sterile powder for reconstitution into a sterile solution or dispersion.

Where desired, tonicity adjusting agents such as sodium chloride, glycerol and various sugars can be added. Stabilisers such as human serum albumin may also be included. The formulation may be preserved by means of a suitable pharmaceutically acceptable preservative such as a paraben, although preferably it is unpreserved.

It is preferred that the toxin is formulated in unit dosage form, for example it can be provided as a sterile solution in a vial, or as a vial or sachet containing a lyophilised powder for reconstituting a suitable carrier such as water for injection.

In one embodiment the toxin, e.g. botulinum toxin A is formulated in a solution containing saline and pasteurised human serum albumin, which stabilises the toxin. The solution is sterile filtered (0.2 micron filter), filled into individual vials and then vacuum dried to give a sterile lyophilised powder. In use, the powder can be reconstituted by the addition of sterile unpreserved normal saline (sodium chloride 0.9% for injection).

In order for the benefits of the invention to be realised, administration of the botulinum toxin should commence before the child has completed its growing period and fixed myostatic contracture has occurred. The benefits of the invention can be maximised by administering the botulinum toxin to the child at an early stage in its growing period, for example before the child reaches the age of six.

The dose of toxin administered to the patient will depend upon the severity of the condition e.g. the number of muscle groups requiring treatment, the age and size of the patient and the potency of the toxin. The potency of the toxin is expressed as a multiple of the LD₅₀ value for the mouse, one "unit" of toxin being defined as being the equivalent amount of toxin that kills 50% of a group of mice. The definition of potency as used hereinafter is the definition currently used in relation to the product marketed by Porton Products Limited. According to this definition, the potency of the botulinum toxin A available from Porton Products Ltd is such that one nanogram contains 40 mouse units (units).

Typically, the dose administered to the patient will be up to about 1000 units, for example up to about 500 units, and preferably in the range from about 80 to about 460 units per patient per treatment, although smaller or larger doses may be administered in appropriate circumstances. The potency of botulinum toxin, and its long duration of action, means that doses will tend to be

administered on an infrequent basis. Ultimately, however, both the quantity of toxin administered, and the frequency of its administration will be at the discretion of the physician responsible for the treatment, and will be commensurate with questions of safety and the effects produced by the toxin.

The invention will now be illustrated in greater detail by reference to the following non-limiting examples which describe the results of clinical studies with botulinum toxin A:

EXAMPLE 1

The Use of Botulinum Toxin A in the Management
Children with Cerebral Palsy

Thirty three children suffering from cerebral palsy, having a mean age of seven years and an age range of two to seventeen years, were selected for participation in a clinical study.

The criteria for inclusion in the study were the presence of dynamic contractures interfering with function, without clinical evidence of fixed myostatic contracture. Before entering the study, all children underwent clinical evaluation, physiotherapist's assessment and parental assessment. All ambulatory patients underwent gait analysis using electrogoniometers. The children entering the study were suffering from spastic tetraplegia, diplegia, hemiplegia or monoplegia.

The hamstrings and/or calf muscles of each patient

were injected with a sterile solution containing the botulinum toxin A (obtained from Porton Products Limited, UK). Total patient doses ranged from 80 units to 460 units (one unit being equivalent to the murine LD₅₀). Before injecting any muscle group, careful consideration was given to the anatomy of the muscle group, the aim being to inject the area with the highest concentration of neuromuscular junctions. Before injecting the muscle, the position of the needle in the muscle was confirmed by putting the muscle through its range of motion and observing the resultant motion of the needle end. General anaesthesia, local anaesthesia and sedation were used according to the age of the patient, the number of sites to be injected and the particular needs of the patient.

Following injection, it was noted that the onset of effects was complete within thirty six to seventy two hours and lasted from six to eighteen weeks. There were no systemic or local side-effects. All but one patient had some reduction in muscle tone; the one failure occurred early in the study and was probably the result of the toxin dosage administered (75 units) being sub-therapeutic. None of the patients developed extensive local hypotonicity. The majority of children had an improvement in function both subjectively and when measured objectively with gait analysis.

Following injection of the calf muscle groups, an assessment was made of the passive dorsiflexion at the ankle. It was found that the younger children displayed a

marked improvement in passive dorsiflexion, but that for children over six years there was little improvement. This was probably due to the dynamic contracture being replaced by a fixed contracture which was unresponsive to any amount of paresis.

CASE STUDY 1

A five year old girl with moderate right hemiplegia underwent gait analysis and, on examination, was found to have dynamic contractures of her calf and hamstrings. Gait analysis recordings of sagittal plane movements (with 95% confidence limits) were made prior to injection and these revealed that throughout the gait cycle, the knee was in excessive flexion. Gait analysis also indicated that she was in equinus throughout the gait cycle.

Following injection, the knee could be extended nearly to neutral during stance and the gait analysis pattern, although still abnormal was much improved. The ankle traces recorded indicated that she was able to dorsiflex her ankle in gait and had developed a normal range of movements.

Gait analysis was also undertaken at four months. At this stage the effects of the toxin had clinically worn off and it was found that the knee flexed to the same extent in swing that it did prior to injection. However, the gain of extension in stance was largely preserved. At the ankle, there was some relapse but there was still a lesser degree of equinus.

CASE STUDY 2

Measurements were made of the maximal extension of the knee in a group of patients who underwent hamstring injection. Prior to injection, they all had some degree of dynamic knee flexion contracture. Four weeks following injection, this showed a highly significant improvement. However, the one patient who was least affected developed recurvatum at the knee following injection. After this, all patients who had a dynamic knee flexion contracture of less than fifteen degrees were excluded from hamstring injection. Only one local side-effect from the treatment was noted and this was a small subcutaneous haematoma which resolved itself in a few days.

Example 2

The Treatment of the Hereditary Spastic Mouse with Botulinum Toxin A

In cerebral palsy there is frequently a failure of muscle growth leading to fixed muscular contracture. This failure has also been demonstrated in the hereditary spastic mouse (Wright J and Rang M The Spastic Mouse. And the search for an animal model of spasticity in human beings) Clin. Orthop. 1990, 253, 12-19.

A study has been carried out to ascertain the effect of Botulinum Toxin A on the growth of longitudinal muscle in the spastic mouse compared with normal siblings. Groups of spastic mice at six days old had one calf muscle injected with either 1.2 units of Botulinum toxin A or

normal saline.

The mice were sacrificed at maturity and the hind limbs dissected to allow measurement of the muscle and bones.

In the control group, the spastic mice had a 13% failure of longitudinal muscle growth compared with their normal siblings. However, the muscles of the spastic mice injected with Botulinum had growth identical to that of their normal siblings. There was no difference in growth between normal mice injected with saline or Botulinum.

It can be concluded that the injection of intramuscular Botulinum toxin during the growth period of the hereditary spastic mouse allows normal longitudinal muscle growth to take place and it is believed that this finding may have significance in the management of cerebral palsy.

The invention has been illustrated by reference to Botulinum toxin A but it should be understood that the invention is not limited to the use of this toxin. For example, other Botulinum toxins may be employed. Moreover, other presynaptic neurotoxins (e.g. of bacterial origin) which act in a manner similar to botulinum toxin may also be used. Also, synthetic analogues of the botulinum toxins may be envisaged wherein the 50 kd chain and/or the 100 kd chain are subjected to amino acid insertions, deletions and/or substitutions and, provided that such analogues retain the general type of activity exhibited by Botulinum toxin A, their use in the manner described

hereinbefore is embraced by the present invention. The invention is also considered to embrace the use of substances structurally dissimilar to Botulinum toxin A, provided that such substances possess a prolonged ability to inhibit or block release of the synaptic vesicles containing acetylcholine.

CLAIMS:

1. The use of a presynaptic neurotoxin for the manufacture of a medicament for the treatment of cerebral palsy in juvenile patients.
2. The use of a presynaptic neurotoxin for the manufacture of a medicament for the promotion of normal muscle growth in a juvenile patient suffering from dynamic contractures due to cerebral palsy.
3. The use according to Claim 1 or Claim 2 wherein the presynaptic neurotoxin is a bacterial neurotoxin.
4. The use according to Claim 3 wherein the bacterial neurotoxin is a botulinum toxin.
5. The use according to Claim 4 wherein the botulinum toxin is botulinum toxin A.
6. The use according to any one of the preceding Claims wherein the medicament is for the treatment of a human up to six years in age.
7. A method of treating a juvenile patient suffering from arrested muscle growth arising from the presence of dynamic contractures of the muscle, which method comprises administering to the patient a therapeutically effective amount of a substance which blocks the release of synaptic vesicles containing acetylcholine.
8. A method of treating a juvenile patient suffering from cerebral palsy, which method comprises

administering to the juvenile patient a therapeutically effective amount of a substance which blocks the release of synaptic vesicles containing acetylcholine.

9. A method of treating a juvenile patient suffering from arrested muscle growth arising from the presence of dynamic contractures of the muscle, which method comprises administering to the patient a therapeutically effective amount of a presynaptic neurotoxin, for example a bacterial neurotoxin such as botulinum toxin.

10. A method of treating juvenile cerebral palsy in a juvenile patient comprising administering to the patient a therapeutically effective amount of a presynaptic neurotoxin, for example a bacterial neurotoxin such as botulinum toxin.

11. A method of promoting normal muscle growth in a juvenile patient suffering from dynamic contractures due to cerebral palsy, which method comprised administering to the juvenile patient a therapeutic amount of a presynaptic neurotoxin, for example a bacterial neurotoxin such as botulinum toxin.

12. A method according to any one of Claims 6 to 11 wherein the juvenile patient is a human up to six years in age.

13. A method according to any one of Claims 6 to 12 wherein the said substance or presynaptic neurotoxin is a botulinum toxin.

14. A method according to Claim 13 wherein the

botulinum toxin is botulinum toxin A.

15. A method according to Claim 13 or Claim 14 wherein the botulinum toxin is administered by intramuscular injection, eg into a spastic muscle.

16. A method according to Claim 13 or Claim 14 wherein the botulinum toxin is administered by intramuscular injection into the calf muscle or hamstring.

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K37/02

II. FIELDS SEARCHEDMinimum Documentation Searched⁷

Classification System

Classification Symbols

Int.Cl. 5

A61K ; C07K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸**III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹**

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	THE NEW ENGLAND JOURNAL OF MEDICINE vol. 324, no. 17, 25 April 1991, BOSTON, MA, US pages 1186 - 1194 J. JANKOVIC ET AL. 'THERAPEUTIC USES OF BOTULINUM TOXIN.' cited in the application see page 1191, right column, line 27 - line 28	1-16
A	ANNALS OF NEUROLOGY vol. 28, no. 4, October 1990, BOSTON, MA, US pages 512 - 515 B.J. SNOW ET AL. 'TREATMENT OF SPASTICITY WITH BOTULINUM TOXIN: A DOUBLE-BLIND STUDY.' see page 515, left column, line 12 - line 19	1-16

¹⁰ Special categories of cited documents:¹⁰ "A" document defining the general state of the art which is not considered to be of particular relevance¹⁰ "E" earlier document but published on or after the international filing date¹⁰ "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)¹⁰ "O" document referring to an oral disclosure, use, exhibition or other means¹⁰ "P" document published prior to the international filing date but later than the priority date claimed¹⁰ "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention¹⁰ "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step¹⁰ "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.¹⁰ "A" document member of the same patent family**IV. CERTIFICATION**

Date of the Actual Completion of the International Search

26 NOVEMBER 1992

Date of Mailing of this International Search Report

18. 12. 92

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

RYCKEBOSCH A.O.

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ **Claims Nos.:**
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 7-16 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ **Claims Nos.:**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ **Claims Nos.:**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.